



King's Research Portal

DOI:

[10.1017/S095457941700164X](https://doi.org/10.1017/S095457941700164X)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Schaefer, J., Scult, M., Caspi, A., Arseneault, L., Belsky, D., Hariri, A., Harrington, H., Ramrakha, S., Richie, P., & Moffitt, T. E. (2017). Is low cognitive functioning a predictor or consequence of major depressive disorder? A test in two longitudinal birth cohorts. *Development and Psychopathology*.
<https://doi.org/10.1017/S095457941700164X>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Is Low Cognitive Functioning a Predictor or Consequence of Major Depressive Disorder? A Test in Two Longitudinal Birth Cohorts

ABSTRACT

Cognitive impairment has been identified as an important aspect of major depressive disorder (MDD). We tested two theories regarding the association between MDD and cognitive functioning using data from longitudinal cohort studies. One theory, the “cognitive reserve hypothesis,” suggests that higher cognitive ability in childhood decreases risk of later MDD. The second, the “scarring hypothesis,” instead suggests that MDD leads to persistent cognitive deficits following disorder onset. We tested both theories in the Dunedin Study, a population-representative cohort followed from birth to midlife and assessed repeatedly for both cognitive functioning and psychopathology. We also used data from the E-Risk Study to test whether childhood cognitive functioning predicts future MDD risk independent of family-wide and genetic risk using a discordant twin design. Contrary to both hypotheses, we found that childhood cognitive functioning did not predict future risk of MDD, nor did Study members with a past history of MDD show evidence of greater cognitive decline *unless* MDD was accompanied by other comorbid psychiatric conditions. Our results thus suggest that low cognitive functioning is related to comorbidity, but is neither an antecedent nor enduring consequence of MDD. Future research may benefit from considering cognitive deficits that occur during depressive episodes from a transdiagnostic perspective.

Keywords: intelligence, depression, cognitive reserve, cognitive scarring, cognitive functioning

INTRODUCTION

Major depressive disorder (MDD) is the most common of all psychiatric disorders and a leading cause of disability worldwide (Whiteford et al., 2013). Although lifetime prevalence rates generated by cross-sectional epidemiologic surveys suggest that roughly a third of a population will develop MDD at some point during the life course (Kessler et al., 2005), corresponding figures drawn from longitudinal studies suggest that the true lifetime prevalence of the disorder may be substantially higher (Farmer, Kosty, Seeley, Olino, & Lewinsohn, 2013; Moffitt et al., 2010; Schaefer et al., 2017). This high prevalence is concerning, as MDD has been shown to predict lower life expectancy, increased susceptibility and risk of mortality from physical disease, and higher risk of suicide (Cassano & Fava, 2002). MDD also negatively affects multiple measures of occupational and interpersonal functioning (Adler et al., 2006; Hirschfeld et al., 2000).

Interestingly, many of these functional impairments associated with MDD have been shown to persist even after patients' depressed mood has remitted (Kennedy, Foy, Sherazi, McDonough, & McKeon, 2007), suggesting that non-affective factors may play a critical role in determining functional outcomes. One such well-established predictor of overall functioning is cognitive functioning. Although deficits in the ability to think or concentrate have been listed among the diagnostic criteria for MDD since the term "major depressive disorder" was first introduced in the mid-1970s (Philipp, Maier, & Delmo, 1991), substantial interest in the treatment of cognitive impairment in the context of MDD has emerged more recently. For example, the National Academies of Sciences have hosted several workshops focused on understanding and treating cognitive dysfunction in depression in recent years (National

Academies of Sciences, Engineering, and Medicine, 2015), and the Food & Drug Administration (FDA) is now considering proposals to approve drugs that specifically target cognitive deficits associated with depression (Ledford, 2016; Mullard, 2016). These initiatives have been motivated by a number of cross-sectional reviews and meta-analyses on MDD, which report (1) that depressed individuals score lower than healthy controls across a wide variety of cognitive tasks (Christensen, Griffiths, Mackinnon, & Jacomb, 1997; Rock, Roiser, Riedel, & Blackwell, 2014; Rogers et al., 2004; Snyder, 2013), even at first episode (Lee, Hermens, Porter, & Redoblado-Hodge, 2012), and (2) that these deficits can be observed even in individuals whose depression has remitted (Bora, Harrison, Yücel, & Pantelis, 2013; Rock et al., 2014). Greater cognitive deficits in the context of MDD, in turn, are associated with increased symptom severity (McDermott & Ebmeier, 2009), higher rates of relapse and recurrence (Majer et al., 2004), and impaired functioning after discharge from psychiatric hospitalization (Jaeger, Berns, Uzelac, & Davis-Conway, 2006). Consequently, there is now considerable interest in the identification of novel therapeutic agents capable of bringing about “cognitive remission” in depressed patients (Bortolato et al., 2016; Ledford, 2016), in addition to the remission of affective symptoms.

Before recommending that cognitive impairment in MDD should become a target of treatment, however, it is important to understand the origin and developmental course of these deficits. To date, two theoretical models have been proposed to explain the relationship between persistent cognitive impairments and MDD. The first, called the “cognitive reserve hypothesis,” suggests that individuals with high intelligence are simply less likely to develop depression, either due to superior neural integrity or an increased ability to cope with or avoid stressful situations (Barnett, Salmond, Jones, & Sahakian, 2006; Koenen et al., 2009; Salmond, Menon, Chatfield, Pickard, & Sahakian, 2006; Scult, Knodt, Swartz, Brigidi, & Hariri, 2016). Thus,

cognitive “deficits” seen in cross-sectional studies that compare the cognitive performance of depressed or remitted individuals to healthy volunteers would be an indicator of “trait-like” differences that present early in development, well before MDD onset. This model draws support from a number of longitudinal studies documenting that low intelligence at time 1 is a robust predictor of subsequent depression at time 2, summarized in a recent meta-analysis (Sculth et al., 2017). Sculth et al. (2017) note, however, that the majority of the studies demonstrating a predictive association between intelligence and MDD appear to be driven by depressive symptoms already present at the time of baseline cognitive assessment.

A second explanatory model, termed the “scarring hypothesis,” suggests that the cognitive deficits observed in depressed patients result from enduring changes in physiology and neurochemistry that begin around the time of MDD onset and impair cognitive functioning from that point forward (Lewinsohn, Steinmetz, Larson, & Franklin, 1981). In this model, cognitive impairment in the context of MDD falls somewhere between “trait” and “state” factors. Although cognitive deficits are not proposed to precede the onset of depressive symptoms, they are hypothesized to persist well *after* the resolution of affective symptoms, potentially leaving MDD patients with a lifelong (albeit mild) impairment.

Although both of these models have been supported by previous research, the existing body of literature on persistent cognitive deficits in MDD is characterized by at least four important limitations. First, many of the studies that report associations between MDD and cognitive functioning have used small, clinical samples. Because depressed individuals receiving psychiatric care may differ from those who are not in several significant ways, the generalizability of these findings to the larger population of depressed individuals is unclear.

This possibility is underscored by a recent study using population-representative data from the National Comorbidity Survey Adolescent Supplement (NCS-A), which reported that adolescents with past-year depression or dysthymia scored *higher* (rather than lower) on a measure of fluid intelligence compared to peers with no distress disorders (Keyes, Platt, Kaufman, & McLaughlin, 2016).

Second, the majority of studies that report associations between IQ and MDD have assessed MDD at only a single time point. However, multiple psychiatric assessments are desirable in this context because longitudinal studies that have calculated the lifetime prevalence of MDD using both single and repeated assessments have generally found that repeated assessments generate 2.5 to 3 times higher prevalence estimates (Moffitt et al., 2010; Takayanagi et al., 2014). Thus, studies that use cognitive functioning to predict MDD at a single point in time are more likely to miscategorize individuals who have experienced or will experience depression as “healthy controls,” potentially biasing estimates of effect size.

Third, it is also desirable to analyze data drawn from studies with multiple cognitive assessments, particularly when evaluating participants for evidence of cognitive “scarring”. Despite this, the majority of studies that examine associations between cognitive performance and remitted depression are cross-sectional in nature, making it difficult to determine whether or not observed deficits represent a true decline from baseline ability following a depressive episode.

Fourth, relatively few studies of the link between IQ and MDD have taken rigorous steps to account for the presence or absence of comorbid diagnoses in diagnostic groups (see Scult et al., 2017), and those that *have* assessed participants for comorbidity have tended to use a single

assessment wave (Snyder, 2013). These designs limit interpretation of previous findings, as prior work has shown that many psychiatric disorders apart from MDD are predicted prospectively by low IQ (Batty, Mortensen, & Osler, 2005; Gale et al., 2010; Gale et al., 2008), associated with contemporaneous impairments in cognitive test performance (Airaksinen, Larsson, & Forsell, 2005; Horner & Hamner, 2002; Muller & Roberts, 2005; Schaefer, Giangrande, Weinberger, & Dickinson, 2013), and associated with cognitive “scarring” that lingers after symptomatic remission (Mann-Wrobel, Carreno, & Dickinson, 2011; Meier et al., 2012, 2014; Stavro, Pelletier, & Potvin, 2013). This raises the possibility that observed deficits thought to be associated with MDD are, in fact, driven by either unobserved comorbidities or some shared, transdiagnostic process.

To address these limitations, we present tests of both the cognitive reserve and scarring hypotheses using data drawn from two population-representative, longitudinal studies. The first sample, the Dunedin Study, follows a population-representative cohort from birth to midlife, with IQ tests administered at ages 7, 9, 11, and 38 years, and neuropsychological testing conducted at ages 13 and 38. At age 38, Dunedin Study members were also administered a set of self- and informant-report questionnaires asking questions about perceived cognitive functioning. In addition, Dunedin Study members completed psychiatric interviews assessing them for a variety of common psychiatric disorders every few years starting at age 11.

Over its course, the Dunedin Study also assessed Study members for a number of clinical indicators relevant to MDD, including disorder age of onset, persistence/recurrence of depressive episodes, self-rated impairment due to MDD, number of MDD diagnostic criteria endorsed, whether the Study member received clinical attention for their MDD, and psychiatric

comorbidity. We used these variables to test whether evidence of cognitive reserve or scarring is especially pronounced among Study members with particularly early-onset, severe, comorbid, or otherwise extreme cases of MDD.

Our second sample, the Environmental Risk (E-Risk) Longitudinal Twin Study, follows a cohort of twins born in the U.K. from birth to age 18 years, with IQ tests administered at age 12 and a single psychiatric assessment using DSM criteria administered at age 18 years. We used the E-Risk Study's twin design to examine whether the lower-IQ member of each twin pair was at relatively elevated risk of receiving a depression diagnosis at age 18. Because this design controls for shared environmental and (in monozygotic twin pairs) genetic factors that might normally account for an association between IQ and MDD, a positive finding would indicate that lower IQ predicts risk of MDD independent of these factors, providing support for a causal relationship.

METHODS

Because our article makes use of data drawn from two different longitudinal studies, we have divided the methods section into two parts. Part I describes the assessment of IQ and mental disorder in the Dunedin Study, whereas Part II describes how these same constructs were assessed in the E-Risk Study. A description of the neuropsychological measures administered to Dunedin Study members at ages 13 and 38 can be found in the Supplementary Materials.

I. The Dunedin Study

Sample

The Dunedin Multidisciplinary Health and Development Study is a 4-decade, longitudinal investigation of health and behavior in a population-representative birth cohort.

Study members ($N = 1,037$; 91% of eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand who were eligible for the longitudinal study based on residence in the province at age 3, and who participated in the first follow-up assessment at age 3. The cohort represents the full range of socioeconomic status on New Zealand's South Island. In adulthood, the cohort matches the New Zealand National Health and Nutrition Survey on health indicators (e.g., BMI, smoking, GP visits) (Poulton, Moffitt, & Silva, 2015). The cohort is primarily white; fewer than 7% self-identify as having partial non-Caucasian ancestry. Assessments were carried out at birth and at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95% of the 1,007 Study Members still alive took part. At each assessment wave, each Study member is brought to the Dunedin research unit for a full day of interviews and examinations. The Otago Ethics Committee approved each phase of the Study and informed consent was obtained from all Study members.

Measures of Intelligence (IQ)

Childhood intelligence. We report results from the Wechsler Intelligence Scale for Children—Revised (WISC-R; Wechsler, 1974), using participants' total scores averaged over the three assessment points at ages 7, 9, and 11 to represent intelligence in childhood.

Adult intelligence. We report results from the Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV; Wechsler, 2008), administered at age 38.

Self-reported cognitive functioning

At age 38, Study members were queried about problems related to memory and attention. Study members reported how often in the past year (never, sometimes, or often) they

experienced problems with keeping track of appointments, remembering why they went to a store, and repeating the same story to someone, among other items. Scores on each of the 17 questions were summed to create an overall measure of cognitive difficulties ($M = 9.1$; $SD = 5.3$; range = 0-31; internal consistency reliability = 0.83). Study members were also asked to rate the extent to which their cognitive difficulties interfered with their lives on a scale from 1 (some impairment) to 5 (severe impairment). Both self-reported cognitive difficulties ($r = -0.15$) and the extent of impairment ($r = -0.16$) were negatively correlated with adult full-scale IQ (both p 's < 0.0001).

Informant-reported cognitive problems

Informant reports of Study members' cognitive function were obtained at age 38. Study members nominated people who "knew them well." These informants were mailed questionnaires and asked to complete a checklist, including whether the Study member had problems with his or her attention and memory over the past year. The informant-reported attention problems scale consisted of four items: "Is easily distracted, gets side-tracked easily," "Can't concentrate, mind wanders," "Tunes out instead of focusing," and "Has difficulty organizing tasks that have many steps" (internal consistency reliability = 0.79). The informant-reported memory problems scale consisted of three items: "Has problems with memory," "Misplaces wallet, keys, eyeglasses, paperwork," and "Forgets to do errands, return calls, pay bills" (internal consistency reliability = 0.64). Both informant-reported attention problems ($r = -0.26$) and informant-reported memory problems ($r = -0.14$) were negatively correlated with adult full-scale IQ (both p 's < 0.0001).

Assessment of Mental Disorders

Mental disorders were ascertained in the Dunedin Study longitudinally using a periodic sampling strategy: Every 2 to 6 years, Study members were interviewed about past-year symptoms in a private in-person interview at the research unit by trained interviewers with tertiary qualifications and clinical experience in a mental health-related field such as family medicine, clinical psychology, or psychiatric social work (i.e. not lay interviewers). Interviewers used the Diagnostic Interview Schedule for Children (DIS-C) at the younger ages (11-15 years) and the Diagnostic Interview Schedule at the older ages (18-38 years). At each assessment, interviewers were kept blind to Study members' previous data, including mental health status. At ages 11, 13, and 15, diagnoses were made according to the then-current DSM-III and grouped for this article into a single wave reflecting the presence or absence of specific juvenile mental disorders. At ages 18 and 21, diagnoses were made according to the DSM-III-R (APA, 1987), and at ages 26, 32, and 38 diagnoses were made according to the DSM-IV (APA, 1994). This method led to 6 waves in total representing ages 11-15, 18, 21, 26, 32, and 38. In addition to symptom criteria, diagnosis required impairment ratings for that disorder ≥ 2 on a scale from 1 (some impairment) to 5 (severe impairment). Each disorder was diagnosed regardless of the presence of other disorders. Variable construction details, reliability and validity, and evidence of life impairment for diagnoses have been reported previously (Feehan, McGee, Raja, & Williams, 1994; Kim-Cohen et al., 2003; Moffitt et al., 2007, 2010; Newman et al., 1996).

II. The Environmental Risk (E-Risk) Cohort

Sample

Participants were members of the Environmental Risk (E-Risk) Longitudinal Twin Study, a birth cohort of 2,232 British children. The sample was drawn from a larger birth register of

twins born in England and Wales from 1994-1995 (Trouton, Spinath, & Plomin, 2002). Full details on the sample have been previously reported (Moffitt & the E-Risk Study Team, 2002). Briefly, the E-Risk sample was constructed in 1999–2000, when 1,116 families (93% of those eligible) with same-sex 5-year-old twins participated in home-visit assessments. This sample comprised 56% monozygotic (MZ) and 44% dizygotic (DZ) twin pairs. Within zygosity, 48% of MZ twins were male, and 50% of DZ twins were male. Families were recruited to represent the UK population of families with newborns in the 1990s, on the basis of residential location throughout England and Wales and mother's age. Teenaged mothers with twins were over-selected to replace high-risk families who were selectively lost to the register through nonresponse. Older mothers having twins via assisted reproduction were under-selected to avoid an excess of well-educated older mothers. The study sample represents the full range of socioeconomic conditions in Great Britain, as reflected in the families' distribution on a neighborhood-level socioeconomic index (ACORN [A Classification of Residential Neighborhoods], developed by CACI Inc. for commercial use) (Odgers, Caspi, Bates, Sampson, & Moffitt, 2012): 25.6% of E-Risk families live in “wealthy achiever” neighborhoods compared to 25.3% nationwide; 5.3% vs. 11.6% live in “urban prosperity” neighborhoods; 29.6% vs. 26.9% live in “comfortably off” neighborhoods; 13.4% vs. 13.9% live in “moderate means” neighborhoods; and 26.1% vs. 20.7% live in “hard-pressed” neighborhoods. E-Risk underrepresents “urban prosperity” neighborhoods because such households are likely to be childless.

Follow-up home visits were conducted when the children were aged 7 (98% participation), 10 (96% participation), 12 (96% participation), and, most recently in 2012–2014, 18 years (93% participation). There were 2,066 children who participated in the E-Risk

assessments at age 18, and the proportions of MZ (56%) and male same-sex (47%) twins were almost identical to those found in the original sample at age 5. The average age of the twins at the time of the assessment was 18.4 years ($SD = 0.36$); all interviews were conducted after the 18th birthday. Home visits at ages 5, 7, 10, and 12 years included assessments with participants as well as their mother (or primary caretaker); the home visit at age 18 included interviews only with the participants. Each twin participant was assessed by a different interviewer.

The Joint South London, Maudsley, and the Institute of Psychiatry Research Ethics Committee approved each phase of the study. Parents gave informed consent and twins gave assent between 5 and 12 years and then informed consent at age 18.

Measure of Intelligence (IQ)

Childhood intelligence. We administered a short version of the Wechsler Intelligence Scale for Children-Revised (WISC-R) when Study members were age 12 years. Using two subtests (Matrix Reasoning and Information), we prorated Study members' IQs and standardized them to $M = 100$ ($SD = 15$), according to the method recommended by Sattler (2008).

Assessment of Depression

Unlike the Dunedin cohort, which underwent repeated diagnostic assessments from age 11 to 38, the E-Risk Study members participated in only one diagnostic interview at age 18, during which they were assessed for past-year DSM-IV symptoms of MDD using the Diagnostic Interview Schedule (DIS) (Robins, Cottler, Bucholz, & Compton, 1995). As in the Dunedin Study, E-Risk Study members meeting symptom criteria for MDD also needed to report

impairment ratings ≥ 2 on a scale from 1 (some impairment) to 5 (severe impairment) to receive a diagnosis.

RESULTS

We present results in three parts. Part I presents our tests of the cognitive reserve hypothesis, in which lower IQ in childhood is hypothesized to predict an increased risk of subsequent MDD. Part II presents our tests of the scarring hypothesis, in which IQ deficits are hypothesized to persist in individuals with a history of MDD, even after remission of their affective symptoms. Finally, Part III extends both of these analyses to neuropsychological measures assessing memory and executive functioning, two domains that have been repeatedly linked to MDD in previous work (Bora et al., 2013; Hsu & Davison, 2017; Rock et al., 2014).

I. The Cognitive Reserve Hypothesis

Does lower IQ in childhood predict increased risk of developing Major Depressive Disorder?

To address this question, we started with 957 (92.3%) of the original 1,037 Dunedin Study members, including only those individuals who (a) had participated in at least half of the six mental health assessment waves from ages 11 to 38 and (b) had available childhood IQ data. Because schizophrenia is often accompanied by depression, and is associated with pronounced pre-morbid and post-onset cognitive deficits as well as thought disorder symptoms (Kendler, Ohlsson, Sundquist, & Sundquist, 2014; Meier et al., 2014; Reichenberg et al., 2010; Schaefer et al., 2013), we further refined our analytic sample by excluding all Study members who received a diagnosis of schizophrenia by age 38 ($N = 37$). This step ensured that any observed associations between MDD and IQ were not driven by these individuals.

Of the remaining 920 Study members, 812 (88.3%) contributed 6 waves of mental health data, 67 (7.3%) contributed 5 waves of mental health data, 26 (2.8%) contributed 4 waves of mental health data, and 15 (1.6%) contributed 3 waves of mental health data. From ages 11 to 38, 431 (46.9%) of these Study members received a diagnosis of major depressive disorder (MDD) at one or more assessment waves. These Study members constituted the “ever-depressed” group. The remainder of the cohort ($N = 489$, 53.2%) did not meet criteria for a diagnosis of MDD between the ages of 11 and 38. These Study members constituted the “never-depressed” group. Together, these groups composed the full analytic sample (**Figure 1A**).

---Figure 1 Here---

As an initial test of the cognitive reserve hypothesis, we conducted a follow-forward analysis using a modified Poisson regression model with robust standard errors to estimate relative risk for the binary outcome of lifetime MDD (Zou, 2004). Methodologists have suggested that risk ratios are less inflated than odds ratios in situations where the outcome is common, which is the case for MDD in our sample (Cummings, 2009). The risk ratios presented can be understood as the ratio change in average risk of MDD for every one point increase in IQ. Using this approach, we found that risk of membership in the ever-depressed ($N = 431$; mean childhood IQ = 100.0, SD = 14.4) versus never-depressed group ($N = 489$; mean childhood IQ = 101.4, SD = 13.8) did not differ as a function of childhood IQ, controlling for sex (IRR = 0.997; 95% CI = 0.992, 1.002; $p = 0.247$).

Previous studies have suggested that low childhood IQ is associated with an increased risk of developing not only depression, but also a number of other psychiatric conditions, including anxiety and substance use disorders (Fergusson, Horwood, & Ridder, 2005; Gale et al.,

2008; Koenen et al., 2009; Rajput et al., 2011). Thus, it is possible that our ability to detect a predictive relationship between childhood IQ and lifetime depression is limited by the presence of other psychiatric disorders in the “never-depressed” group. Fortunately, one advantage afforded by the Dunedin Study’s repeated mental health assessments is that they allowed us to identify the small group of individuals who have never met criteria for *any* of the mental disorders assessed by the Study (hereafter referred to as the “enduring-mental-health” group; Schaefer et al., 2017), and to use these Study members as a new comparison group ($N = 161$ who had childhood IQ data; mean childhood IQ = 102.3, $SD = 14.0$) (**Figure 1A**). We thus conducted an additional follow-forward analysis to test whether childhood IQ was a significant predictor of membership in the ever-depressed versus enduring-mental-health groups, controlling for sex. Consistent with our previous results, we found that childhood IQ still did not appear to distinguish between the two groups ($IRR = 0.997$; 95% $CI = 0.994, 1.001$; $p = 0.136$).

To provide a point of comparison, we also tested whether childhood IQ was a significant predictor of membership in the small group of Study members with schizophrenia ($N = 37$; mean childhood IQ = 94.0, $SD = 17.6$) versus the majority of the cohort who were never diagnosed with schizophrenia ($N = 920$; mean childhood IQ = 100.7, $SD = 14.1$), controlling for sex. Here, low childhood IQ *was* associated with higher risk of receiving a schizophrenia diagnosis ($IRR = 0.968$; 95% $CI = 0.944, 0.992$; $p = 0.010$).

Does lower IQ in childhood exert an effect on an individual’s later risk of developing Major Depressive Disorder independent of family-wide and genetic risk?

An even more powerful approach to testing the cognitive reserve hypothesis is to compare two children growing up in the same family. If the cognitive reserve hypothesis is

correct, the sibling with higher IQ should be at lower risk of developing MDD. We tested this hypothesis in E-Risk Longitudinal Twin Study the using the following mixed-effects model:

$$\text{logit}(\pi_{ij}) = \beta_0 + \beta_w(X_{ij} - \bar{X}_i) + \beta_B \bar{X}_i$$

In this specification, IQ effects are parsed into *between-twin pair effects* and *within-twin pair effects* using a logistic regression model, where i is used to index twin pairs and j represents individual twins within pairs, so π_{ij} and X_{ij} represent, respectively, the probability of receiving a depression diagnosis and childhood IQ values for the j^{th} twin of the i^{th} pair, whereas \bar{X}_i represents the mean childhood IQ of both twins within the i^{th} pair. The between-twin pair regression coefficient (β_B) estimates whether pairs of twins with higher average age-12 IQ are at lower risk of being diagnosed with MDD at age 18. In contrast, the within-twin pair regression coefficient (β_w) estimates whether the twin with higher IQ than his or her co-twin is less likely to be diagnosed with MDD than his or her co-twin.

We first estimated this model using data from all available twin pairs (MZ and DZ) in E-Risk. A significant between-twin-pair effect would reflect family-wide factors common to both twins that influence IQ and MDD and may underlie their association. A significant within-twin-pair effect, on the other hand, would indicate that possessing low IQ in childhood predicts MDD independent of any factors that are shared between siblings growing up in the same family (Carlin et al., 2005). We then estimated this model using only the MZ twin pairs in the E-Risk Study. Because MZ twins are genetically identical, a significant within-twin pair effect would rule out the possibility that the association between IQ and MDD arises solely due to a shared genetic susceptibility that elevates risk of both phenotypes.

The parameters estimated from each of these models are reported in **Table 1**. Of the original 2,232 Study members, we included 2,003 (89.7%), excluding twins if they belonged to a twin pair in which (a) 1 or more twins lacked IQ data at age 12, or (b) both twins lacked mental health assessment data at age 18. Of these 2,003 Study members, 404 (20.2%) received a diagnosis of MDD. Both the full-cohort and MZ-twin-only models indicated that neither between-twin-pair nor within-twin-pair differences in IQ tested at age 12 appear to predict risk of MDD at age 18, consistent with our results from the follow-forward analysis conducted in the Dunedin Cohort. These findings did not support the assumption that lower IQ is causally related to increased risk of subsequent depression.

---Table 1 Here---

Could lower IQ in childhood predict particularly early-onset or severe MDD?

Although childhood IQ did not predict risk of future MDD in either cohort, it is still possible that a predictive relationship might exist between IQ in childhood and specific types of MDD, especially given previous research indicating a link between lower cognitive functioning and higher rates of relapse/recurrence, increased symptom severity, and impaired global functioning among depressed individuals (Jaeger et al., 2006; Majer et al., 2004; McDermott & Ebmeier, 2009). Thus, we next tested the hypotheses that childhood IQ would predict measures of MDD age-of-onset, persistence, self-rated impairment, number of diagnostic criteria endorsed, clinical attention, or psychiatric comorbidity in the Dunedin Cohort.

Age of onset. We tested whether childhood IQ predicted an earlier age of depression onset by conducting a Cox proportional hazards regression using data from the full analytic

sample ($N = 920$), controlling for sex. We recorded the assessment wave during which each Study member in the ever-depressed group received his or her first diagnosis of MDD as the age of depression onset ($M = 23.3$, $SD = 7.0$, range = 15-38). We found that childhood IQ did not significantly predict depression age of onset ($HR = 1.00$; 95% CI = 0.99, 1.00; $p = 0.381$), indicating that Study members with low IQ did not appear to develop depression any earlier than Study members with higher IQ.

Persistent course. We calculated depression recurrence/persistence for each Study member in the ever-depressed group ($N = 431$) as the *proportion* of waves during which that Study member met diagnostic criteria for MDD ($M_{\text{proportion}} = 0.30$, $SD = 0.16$, range = 0.17-1.00). We then conducted a linear regression that predicted the proportion of waves each Study member had received an MDD diagnosis as a function of childhood IQ, controlling for sex. We found no significant association between childhood IQ and this measure ($b = -0.001$; 95% CI: -0.002, 0.000; $t(428) = -1.31$; $p = 0.19$), indicating that Dunedin Study members with low IQ who were diagnosed with MDD did not appear to spend significantly more Study waves suffering from depression than their higher-IQ peers with MDD.

Self-rated impairment. Dunedin Study members were asked to rate the functional impairment caused by their depressive symptoms on a scale from 1 (some impairment) to 5 (severe impairment) at each assessment wave between the ages of 18 and 38. We recorded self-rated impairment in this cohort as the maximum impairment rating given between the ages of 18 and 38 ($M = 4.05$, $SD = 0.88$, range = 2-5) by each Study member who met diagnostic criteria for MDD at least once during this same period ($N = 412$). We limited our analysis of impairment to this age range because self-ratings of impairment were not collected in earlier assessments.

We conducted a linear regression model predicting self-rated impairment as a function of childhood IQ, controlling for sex. We found that childhood IQ was a significant predictor of self-rated impairment ($b = -0.01$; 95% CI: $-0.01, 0.00$; $t(409) = -2.05$; $p = 0.041$), suggesting that individuals with lower IQs who develop MDD tend to rate their depression as more impairing than their higher-IQ peers with MDD. Such an effect is likely to be of little practical significance, however, as each 1-point increase in IQ is associated with a predicted decrease of only $1/100^{\text{th}}$ of a point on a 5-point self-rated impairment scale.

Symptom count. We calculated symptom count as the number of MDD criteria endorsed by Study members between the ages of 18 and 38 ($M = 15.03$, $SD = 7.78$, range = 4-41) by each Study member who met diagnostic criteria for MDD at least once during this same period ($N = 413$). We limited our analysis of symptom criteria to this age range because symptom count data from earlier waves were not available.

We conducted a linear regression predicting symptom count between the ages of 18 and 38 as a function of childhood IQ, controlling for sex. We found no significant association between childhood IQ and this measure ($b = -0.02$; 95% CI: $-0.07, 0.03$; $t(410) = -0.86$; $p = 0.392$), suggesting that Study members with lower IQs tended to endorse a similar number of MDD symptoms relative to Study members with higher IQs.

Clinical attention. Dunedin Study members reported if they had contacted a professional (i.e. a general practitioner, psychologist, or psychiatrist) for a mental health problem or received psychiatric medication between the ages of 20 and 38. Of the 350 Study members diagnosed with MDD during this same period in the full analytic sample (with present treatment contact data), 249 (71.1%) endorsed some form of treatment contact. We conducted a Poisson regression

model with robust standard errors to calculate risk ratios for the binary outcome of treatment contact as a function of childhood IQ, controlling for sex. We found no significant association between childhood IQ and this measure (IRR = 1.002; 95% CI: 0.997, 1.006; $p = 0.464$), suggesting that individuals with lower IQs who develop MDD were no more likely to receive treatment than their higher-IQ peers with MDD.

Comorbidity. In the Dunedin Study, we operationalized comorbidity as the number of diagnostic families (including depressive disorders, anxiety disorders, substance use disorders, attention-deficit/hyperactivity disorder, and conduct disorder) represented in a Study member's complete history of psychiatric diagnoses accumulated between the ages of 11 and 38 years ($M = 1.70$, $SD = 1.21$, range 0-5 in the full analytic sample; $M = 2.54$, $SD = 0.97$, range 1-5 in the ever-depressed group). We did not include schizophrenia in our count of psychiatric comorbidities because Study members who developed schizophrenia were excluded from the analytic sample.

We tested the association between childhood IQ and lifetime psychiatric comorbidity using a Poisson regression model that predicted the count of diagnostic families represented in each Study member's diagnostic history between the ages of 11 and 38 as a function of childhood IQ, controlling for sex. We found an association between childhood IQ and comorbidity in both the full analytic sample ($N = 920$; IRR = 0.993; 95% CI: 0.989, 0.996; $p < 0.001$), and among ever-depressed Study members ($N = 431$; IRR = 0.995; 95% CI: 0.991, 0.999; $p = 0.025$).

Figure 2A charts mean IQ as a function of psychiatric comorbidity in the context of MDD. Here we plot IQ scores for Dunedin Study members who have never had depression,

Study members who have had depression only, and Study members who have had depression alongside 1 or more additional psychiatric conditions. **Figure 2A** shows that early IQ deficits were pronounced only among depressed Study members with multiple psychiatric comorbidities. Interestingly, Dunedin Study members with “pure” depression—that is, those who were diagnosed *only* with depression between the ages of 11 and 38 years—appeared to have slightly higher IQs in childhood than Study members who were never diagnosed with depression. We confirmed this observation through follow-forward analysis using Poisson regression, which indicated that Dunedin Study members with higher IQs were more likely to experience pure depression than no depression at all, controlling for sex ($N = 543$; $IRR = 1.019$; 95% $CI = 1.001, 1.037$; $p = 0.040$).

---Figure 2 Here---

Finally, we used modified Poisson regression with robust standard errors to test whether low childhood IQ predicted the emergence of certain types of lifetime psychiatric comorbidities, but not others. We found that children who went on to develop MDD ($N = 420$) with lower childhood IQs were also at increased risk of developing anxiety disorders ($IRR = 0.993$; 95% $CI = 0.989, 0.996$; $p < 0.001$), attention-deficit/hyperactivity disorder ($IRR = 0.949$; 95% $CI = 0.929, 0.969$; $p < 0.001$), and conduct disorder ($IRR = 0.983$; 95% $CI = 0.971, 0.996$; $p = 0.008$), but not substance use disorders ($IRR = 0.999$; 95% $CI = 0.993, 1.006$; $p = 0.861$).

II. *The Scarring Hypothesis*

Are individuals with a history of MDD more likely to show evidence of or report lingering cognitive impairment as adults?

We next used data from the Dunedin Study to test for enduring cognitive deficits in previously-depressed Study members whose MDD had remitted by age 38, the time of adult cognitive assessment. Evidence of intellectual decline among these remitted individuals could be interpreted as evidence of a lingering depression-induced “scar” on cognitive functioning (Lewinsohn et al., 1981). For these analyses, we used data from 744 Study members who were assessed for mental disorder at age 38 but who did not meet criteria for a diagnosis of past-year MDD at age 38. This decision allowed us to separate the lingering cognitive “scarring” effects of a diagnostic history of MDD from the contemporaneous effects of a current episode of MDD. Similar to previous analyses, we also required these individuals to have (a) participated in at least half of the six mental health assessment waves from ages 11 to 38, (b) available childhood and adult IQ data, and (c) never received a diagnosis of schizophrenia. These individuals were divided into two groups: those with a previous history of MDD ($N = 277$; mean adult IQ = 101.2, $SD = 14.4$), and those with no previous history of MDD ($N = 467$; mean adult IQ = 101.0, $SD = 14.4$) (**Figure 1B**).

We conducted a series of one-way ANOVAs testing whether Study members with a previous history of MDD differed from Study members without such a history on age-38 IQ, self-reported cognitive functioning, or informant-reported cognitive functioning, controlling for sex. As shown in **Table 2**, we found that Study members with a history of depression scored lower on our *subjective* measures of cognitive functioning (i.e., self- and informant-report), but not on any of our *objective* measures of cognitive functioning (i.e. WISC-R and WAIS-IV IQ, IQ change from childhood to adulthood). Taken together, these results suggest that Study members with a history of depression were more likely to report that their cognitive functioning was

impaired despite little to no measurable change (on average) in objective cognitive functioning as assessed by IQ tests.

---Table 2 Here---

Is there evidence of cognitive scarring following an episode of particularly severe or early-onset MDD?

One criticism of the analyses summarized in **Table 2** is that, in comparing only those individuals who were *not* depressed at age 38, we potentially ignore many of the most severe, chronic cases of MDD who continued to meet diagnostic criteria at the age-38 assessment wave. Consequently, we next tested whether any of our six clinical indicators (i.e., MDD age-of-onset, persistence/recurrence, self-rated impairment, number of diagnostic criteria endorsed, clinical attention, and comorbidity) predicted change in IQ from childhood (ages 7-11) to adulthood (age 38). If cognitive scarring is more common following severe or early-onset cases of MDD, higher scores on these indicators should predict a more severe decline in IQ following a depressive episode.

As shown in **Table 3**, only psychiatric comorbidity was found to predict a steeper decline in IQ from childhood to adulthood. This finding suggests that the cognitive scarring reported following a depressive episode may be more attributable to disorders commonly comorbid with MDD rather than the experience of a depressive episode per se. **Figure 2B** charts mean change in IQ between childhood (ages 7-11) and adult (age 38) assessments as a function of psychiatric comorbidity in the context of MDD, whereas **Figure 2C** does the same with each of our four subjective measures of cognitive functioning. Consistent with **Figure 2A**, **Figures 2B** and **2C**

show that evidence of IQ decline and high subjective impairment was apparent only for depressed Study members with multiple psychiatric comorbidities.

---Table 3 Here---

III. Beyond IQ

A second potential criticism of the analyses presented in this paper is that IQ is too crude or too global of a measure to detect the subtle changes in cognitive functioning associated with MDD. This may be particularly true for tests of the scarring hypothesis, as previous work has suggested that scarring is most noticeable in the domains of executive functioning (e.g., working memory, attention regulation, inhibitory control, and cognitive flexibility/switching) and long-term memory (Bora et al., 2013; Rock et al., 2014). To address this concern, we selected from our datasets the measures most closely associated with these cognitive domains. A detailed description of these measures can be found in the **Supplementary Materials**.

We first used Poisson regression with robust standard errors to test whether childhood scores on our neuropsychological measures were significant predictors of future MDD in the Dunedin Study, controlling for sex (a further test of the “cognitive reserve hypothesis”). Because Study members completed neuropsychological testing at age 13, we removed individuals who received a diagnosis of MDD during our first, juvenile assessment wave (ages 11 to 15) from the full analytic sample (shown in **Figure 1A**) in order to ensure that scores predicted future, rather than concurrent, MDD. As shown in **Supplementary Table 1**, the association between MDD status and performance on Trails B was marginally significant (IRR = 1.00; 95% CI: 1.00, 1.01;

$p = 0.053$), but otherwise we found little evidence to suggest that any of these measures significantly predicted future MDD risk.

We next conducted a series of one-way ANOVAs testing whether Study members with a previous history of MDD differed from Study members without such a history on neuropsychological measures of executive functioning and memory administered at age 38, controlling for sex (a further test for cognitive scarring). As shown in **Supplementary Table 2**, Study members with a history of MDD scored significantly lower than Study members without such a history on a measure involving the delayed recall of multiple word pairs (WMS-IV Verbal Paired Associates) ($F(1, 738) = 4.40, p = 0.036$). However, this difference did not survive correction for multiple comparisons and no other significant between-group differences were observed. Viewed as a whole, our results provide little support for the notion that lower performance on measures of executive functioning or memory are predictors or enduring consequences of MDD.

DISCUSSION

Contrary to prior research, the present study found little evidence to suggest that low cognitive functioning is either a predictor or an enduring consequence of a major depressive episode. We repeatedly found that associations between cognitive functioning and MDD were evident only in the context of comorbid psychiatric diagnoses. The finding was true for both objective measures of cognitive functioning (i.e., WISC-R and WAIS-IV IQ, IQ change) and for self- and informant-reported indices of cognitive impairment. This pattern of findings suggests that, to the extent that evidence of cognitive reserve or cognitive scarring in MDD exists, it

seems to be largely attributable to psychiatric comorbidities rather than to depressive symptoms per se.

The first hypothesis tested in the present study—the cognitive reserve hypothesis—suggested that individuals with lower cognitive functioning in childhood would be at increased risk of developing MDD later in life. However, childhood IQ did not predict risk of future MDD between the ages of 11 and 38 in the Dunedin Study, even when we compared individuals who developed MDD to those who experienced no diagnosable psychopathology of any sort. Similarly, Study members' performance on specific measures of memory and executive functioning at age 13 also did not predict future risk of MDD. In addition, we found no evidence that childhood IQ predicted MDD risk independent of family-wide and genetic risk when comparing E-Risk Study twins discordant for IQ. Together, these findings indicate that low IQ in childhood does not meaningfully increase risk of a depressive episode between early adolescence and midlife in these two cohorts from different eras and countries.

The second hypothesis tested in this paper—the scarring hypothesis—suggests that the experience of MDD is associated with cognitive impairments that persist even after affective symptoms have remitted. Surprisingly, in remitted Study members we found little to no difference in mean childhood IQ, adult IQ, IQ change, or adult neuropsychological test scores between those with and without a past history of MDD, suggesting that the scarring effects of a depressive episode are not readily detected by these objective measures. However, we also found that those with an MDD history (and their informants) reported significantly greater subjective cognitive impairment than those without such a history.

The finding of greater subjective cognitive impairment in the context of no measurable *objective* deficit suggests at least two possible explanations. First, it is possible that any “lingering” cognitive impairments attributable to a history of MDD are largely subjective in nature. If this were true, the greater self-rated impairment reported by individuals with a history of MDD could reflect either (a) a tendency towards negative self-evaluation commonly seen in individuals vulnerable to depressive episodes, or (b) a form of the “good ol’ days bias,” in which individuals tend to view themselves as having been healthier (e.g., more cognitively advantaged) prior to a negative event (e.g., a depressive episode) (Iverson, Lange, Brooks, & Rennison, 2010). The greater informant-rated impairment, in turn, could be caused by Study members communicating these beliefs to their informants.

A second possibility, however, is that the cognitive deficits that either predispose individuals to depression or follow a depressive episode are contextual in nature. In other words, because formal cognitive testing is designed to measure patients’ optimal cognitive functioning under ideal conditions in the clinic, IQ and other neuropsychological tests may fail to capture genuine impairments that occur only under real-world conditions of high arousal, distraction, or affective distress in vulnerable individuals (i.e., those with a history of depression). The results of the present study do not, therefore, necessarily indicate that reports of cognitive impairment following a depressive episode are solely a product of patients’ cognitive distortions.

Results presented here differ from those of ancillary analyses featured in previous papers that also used data from the Dunedin Study, which reported weak but statistically significant associations between IQ and MDD (Koenen et al., 2009; Meier et al., 2014). These papers, however, like others in the literature, did not control for comorbidity when estimating the

association between IQ and MDD. Moreover, the fact that results can differ even in the same sample speaks to the fact that correlations between IQ and MDD are ephemeral and depend heavily on a study's analytical design and comparison groups.

To some, the proportion of Dunedin Study members diagnosed with MDD may seem unusually high, raising concerns about the representativeness of our sample. However, we have shown elsewhere that (a) the past-year prevalence rates of mental disorders in the Dunedin cohort are similar to prevalence rates in nationwide surveys of the United States and of New Zealand (Moffitt et al., 2010) and (b) that lifetime prevalence estimates of Axis-I mental disorders in the Dunedin Study are comparable to estimates calculated in other cohorts with repeated psychiatric assessments (Schaefer et al., 2017). These observations indicate that the high lifetime prevalence rate of MDD reported here is due primarily to the advantage of our prospective assessment method rather than to an overabundance of mental disorder in New Zealand, or in this cohort.

Despite the methodological advantages provided by our two cohorts, we acknowledge limitations. First, although our study features results from two independent samples, the E-Risk Study did not contain enough psychiatric assessment waves for us to replicate the analyses conducted using the Dunedin Cohort. Thus, it will be important to test the extent to which our findings generalize across different populations in future studies—particularly those findings that relate to lifetime history of disorder.

Second, Study members were assessed for past-year (rather than *current*) depressive symptoms. Moreover, Dunedin Study members tend to schedule data collection when they feel well, reducing the likelihood of acute depressive symptoms on the day of cognitive testing. This

design feature meant that we were unable to control for baseline depressive symptoms at the time of cognitive assessment in our follow-forward analyses. However, given that no association was observed between childhood cognitive functioning and later MDD, it is unlikely that this would alter our conclusions. In addition, we were not able to examine the extent to which MDD was associated with short-term, contemporaneous decreases in cognitive functioning—an important question for future research.

Third, assessment of mental disorder in the Dunedin cohort is both left- and right-hand censored, which means we cannot assess the relationship between IQ and episodes of MDD that occurred prior to age 11, or future cases that may onset after our most recent assessment at age 38. This limitation means that we are not able to comment on the extent to which either childhood-onset or late-onset depression are associated with childhood IQ, or the extent to which such episodes might “scar” future cognitive functioning.

In spite of these limitations, our results have implications for the study and treatment of depression. In particular, they suggest that the persistent cognitive deficits commonly associated with MDD may not be attributable to depression per se, but rather to other psychiatric conditions that frequently co-occur with MDD (Kessler et al., 2003; Melartin et al., 2002). Previous studies comparing the premorbid IQs of individuals who developed MDD to those who did not have found individuals with MDD had premorbid IQs approximately 3 points lower than healthy controls (Sørensen, Sæbye, Urfer-Parnas, Mortensen, & Parnas, 2012), which is comparable to the effect of comorbidity reported in the present study. These findings also shed light on some of the questions highlighted in recent workshops hosted by the National Academies of Sciences (National Academies of Sciences, Engineering, and Medicine, 2015), and suggest that

researchers interested in treating the cognitive deficits associated with depression should perhaps widen their focus to consider alterations in fear-learning, attention, and executive functioning common to multiple disorders.

Our results further suggest that investigators seeking to demonstrate the existence of cognitive impairment in the context of a particular disorder should carefully assess participants for current and past psychiatric comorbidities. This step allows investigators to distinguish between impairments that are attributable to the disorder of interest versus other, comorbid conditions or some shared, transdiagnostic process.

Our findings also have implications for the prevention and treatment of MDD. Our finding that low childhood IQ does not appear to predict the development of MDD suggests that low IQ should not be considered a risk factor for MDD. Similarly, our finding that even the most severely disordered individuals (diagnosed with MDD and 3+ comorbidities) scored only about 5 points lower, on average, than those with no history of depression, indicates that our ability to predict the course of any one person's MDD based on premorbid intelligence is limited at best. Nevertheless, because subjective ratings of Study members' cognitive impairment tended to increase with each additional psychiatric comorbidity, it may be helpful to screen individuals who report ongoing cognitive impairment following a depressive episode for past and current anxiety, substance-use, attention-deficit, or psychotic disorders. In addition, such patients may benefit from cognitive therapy that examines the function and impact of beliefs of cognitive impairment, as well as therapies aimed at regulating affect and managing psychiatric symptoms, which may continue to impact cognitive functioning in certain contexts (e.g., when multi-tasking or under conditions of high emotional arousal).

In summary, we find that cognitive deficits are neither an antecedent nor enduring consequence of MDD, absent psychiatric comorbidities. Thus, future research that seeks to assess and treat cognitive scarring in the context of psychiatric illness would be wise to investigate psychopathology broadly rather than MDD specifically. In addition, rather than focusing on cognitive impairment as a risk factor for MDD or a lingering consequence of the disorder, our results suggest that treatment and prevention efforts should focus on evaluating—and perhaps treating—cognitive deficits that co-occur with depressive symptoms. We hope that our findings will inform studies aiming to develop treatments for these impairments, as well as spur additional research dedicated to better understanding the complex interplay between affective symptoms and cognitive functioning in the individuals who suffer from this disorder.

REFERENCES

- Adler, D. A., McLaughlin, T. J., Rogers, W. H., Chang, H., Lapitsky, L., & Lerner, D. (2006). Job performance deficits due to depression. *American Journal of Psychiatry*, 163(9), 1569–1576. <https://doi.org/10.1176/ajp.2006.163.9.1569>
- Airaksinen, E., Larsson, M., & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. *Journal of Psychiatric Research*, 39(2), 207–214. <https://doi.org/10.1016/j.jpsychires.2004.06.001>
- APA (1987). *Diagnostic and statistical manual of mental disorders: DSM-III-R* (3rd ed., rev.). Washington, DC: American Psychiatric Association.
- APA (1994). *Diagnostic and statistical manual of mental disorders*. (4th ed.). Washington, DC: American Psychiatric Association,.
- Barnett, J. H., Salmond, C. H., Jones, P. B., & Sahakian, B. J. (2006). Cognitive reserve in neuropsychiatry. *Psychological Medicine*, null(08), 1053–1064. <https://doi.org/10.1017/S0033291706007501>
- Batty, G. D., Mortensen, E. L., & Osler, M. (2005). Childhood IQ in relation to later psychiatric disorder: Evidence from a Danish birth cohort study. *The British Journal of Psychiatry*, 187(2), 180–181.
- Bora, E., Harrison, B. J., Yücel, M., & Pantelis, C. (2013). Cognitive impairment in euthymic major depressive disorder: A meta-analysis. *Psychological Medicine*, 43(10), 2017–2026. <https://doi.org/10.1017/S0033291712002085>

- Bortolato, B., Miskowiak, K. W., Köhler, C. A., Maes, M., Fernandes, B. S., Berk, M., & Carvalho, A. F. (2016). Cognitive remission: a novel objective for the treatment of major depression? *BMC Medicine*, 14, 9. <https://doi.org/10.1186/s12916-016-0560-3>
- Carlin, J. B., Gurrin, L. C., Sterne, J. A., Morley, R., & Dwyer, T. (2005). Regression models for twin studies: a critical review. *International Journal of Epidemiology*, 34(5), 1089–1099. <https://doi.org/10.1093/ije/dyi153>
- Cassano, P., & Fava, M. (2002). Depression and public health: An overview. *Journal of Psychosomatic Research*, 53(4), 849–857. [https://doi.org/10.1016/S0022-3999\(02\)00304-5](https://doi.org/10.1016/S0022-3999(02)00304-5)
- Christensen, H., Griffiths, K., Mackinnon, A., & Jacomb, P. (1997). A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *Journal of the International Neuropsychological Society*, 3(6), 631–651.
- Cummings, P. (2009). The relative merits of risk ratios and odds ratios. *Archives of Pediatrics & Adolescent Medicine*, 163(5), 438–445. <https://doi.org/10.1001/archpediatrics.2009.31>
- Farmer, R. F., Kosty, D. B., Seeley, J. R., Olino, T. M., & Lewinsohn, P. M. (2013). Aggregation of lifetime axis I psychiatric disorders through age 30: Incidence, predictors, and associated psychosocial outcomes. *Journal of Abnormal Psychology*, 122(2), 573–586. <https://doi.org/10.1037/a0031429>
- Feehan, M., McGee, R., Raja, S. N., & Williams, S. M. (1994). DSM-III-R disorders in New Zealand 18-year-olds. *Australian and New Zealand Journal of Psychiatry*, 28(1), 87–99. <https://doi.org/10.3109/00048679409075849>
- Fergusson, D. M., John Horwood, L., & Ridder, E. M. (2005). Show me the child at seven II: childhood intelligence and later outcomes in adolescence and young adulthood. *Journal*

- of Child Psychology and Psychiatry*, 46(8), 850–858. <https://doi.org/10.1111/j.1469-7610.2005.01472.x>
- Gale, C. R., Batty, G. D., Tynelius, P., Deary, I. J., & Rasmussen, F. (2010). Intelligence in early adulthood and subsequent hospitalization for mental disorders. *Epidemiology*, 21(1), 70–77.
- Gale, C. R., Deary, I. J., Boyle, S. H., Barefoot, J., Mortensen, L. H., & Batty, G. (2008). Cognitive ability in early adulthood and risk of 5 specific psychiatric disorders in middle age: The Vietnam Experience study. *Archives of General Psychiatry*, 65(12), 1410–1418. <https://doi.org/10.1001/archpsyc.65.12.1410>
- Hirschfeld, R. M. A., Montgomery, S. A., Keller, M. B., Kasper, S., Schatzberg, A. F., Moller, H.-J., ... Versiani, M. (2000). Social functioning in depression: A review. *The Journal of Clinical Psychiatry*, 61(4), 268–275.
- Horner, M. D., & Hamner, M. B. (2002). Neurocognitive functioning in posttraumatic stress disorder. *Neuropsychology Review*, 12(1), 15–30. <https://doi.org/http://dx.doi.org.proxy.lib.duke.edu/10.1023/A:1015439106231>
- Hsu, K. J., & Davison, G. C. (2017). Compounded deficits: The association between neuropsychological impairment and attention biases in currently depressed, formerly depressed, and never depressed individuals. *Clinical Psychological Science*, 5(2), 286–298. <https://doi.org/10.1177/2167702617692998>
- Iverson, G. L., Lange, R. T., Brooks, B. L., & Rennison, V. L. A. (2010). “Good old days” bias following mild traumatic brain injury. *The Clinical Neuropsychologist*, 24, 17–37. <https://doi.org/10.1080/13854040903190797>

- Jaeger, J., Berns, S., Uzelac, S., & Davis-Conway, S. (2006). Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Research*, 145(1), 39–48.
<https://doi.org/10.1016/j.psychres.2005.11.011>
- Kendler, K. S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2014). IQ and schizophrenia in a Swedish national sample: Their causal relationship and the interaction of IQ with genetic risk. *American Journal of Psychiatry*, 172(3), 259–265.
<https://doi.org/10.1176/appi.ajp.2014.14040516>
- Kennedy, N., Foy, K., Sherazi, R., McDonough, M., & McKeon, P. (2007). Long-term social functioning after depression treated by psychiatrists: a review. *Bipolar Disorders*, 9(1–2), 25–37. <https://doi.org/10.1111/j.1399-5618.2007.00326.x>
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., ... Wang, P. S. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*, 289(23), 3095–105.
<https://doi.org/10.1001/jama.289.23.3095>
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62(6), 593–602.
<https://doi.org/10.1001/archpsyc.62.6.593>
- Keyes, K. M., Platt, J., Kaufman, A. S., & McLaughlin, K. A. (2016). Association of fluid intelligence and psychiatric disorders in a population-representative sample of U. S. adolescents. *JAMA Psychiatry*. <https://doi.org/10.1001/jamapsychiatry.2016.3723>
- Kim-Cohen, J., Caspi, A., Moffitt, T. E., Harrington, H., Milne, B. J., & Poulton, R. (2003). Prior juvenile diagnoses in adults with mental disorder: Developmental follow-back of a

- prospective-longitudinal cohort. *Archives of General Psychiatry*, 60(7), 709–717.
<https://doi.org/10.1001/archpsyc.60.7.709>
- Koenen, K. C., Moffitt, T. E., Roberts, A. L., Martin, L. T., Kubzansky, L., Harrington, H., ... Caspi, A. (2009). Childhood IQ and adult mental disorders: A test of the cognitive reserve hypothesis. *American Journal of Psychiatry*, 166(1), 50–57.
<https://doi.org/10.1176/appi.ajp.2008.08030343>
- Ledford, H. (2016). Drugmakers target depression's cognitive fog. *Nature*, 530(7588), 17–17.
<https://doi.org/10.1038/530017a>
- Lee, R. S. C., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode major depressive disorder. *Journal of Affective Disorders*, 140(2), 113–124. <https://doi.org/10.1016/j.jad.2011.10.023>
- Lewinsohn, P. M., Steinmetz, J. L., Larson, D. W., & Franklin, J. (1981). Depression-related cognitions: Antecedent or consequence? *Journal of Abnormal Psychology*, 90(3), 213–219. <https://doi.org/10.1037//0021-843X.90.3.213>
- Majer, M., Ising, M., Künzel, H., Binder, E. B., Holsboer, F., Modell, S., & Zihl, J. (2004). Impaired divided attention predicts delayed response and risk to relapse in subjects with depressive disorders. *Psychological Medicine*, null(08), 1453–1463.
<https://doi.org/10.1017/S0033291704002697>
- Mann-Wrobel, M. C., Carreno, J. T., & Dickinson, D. (2011). Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. *Bipolar Disorders*, 13(4), 334–342.
<https://doi.org/10.1111/j.1399-5618.2011.00935.x>

- McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders, 119*(1–3), 1–8.
<https://doi.org/10.1016/j.jad.2009.04.022>
- Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. E., ... Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences of the United States of America, 109*(40), E2657–E2664. <https://doi.org/10.1073/pnas.1206820109>
- Meier, M. H., Caspi, A., Reichenberg, A., Keefe, R. S. E., Fisher, H. L., Harrington, H., ... Moffitt, T. E. (2014). Neuropsychological decline in schizophrenia from the premorbid to the post-onset period: Evidence from a population-representative longitudinal study. *American Journal of Psychiatry, 171*(1), 91–101.
<https://doi.org/10.1176/appi.ajp.2013.12111438>
- Melartin, T. K., Rytälä, H. J., Leskelä, U. S., Lestelä-Mielonen, P. S., Sokero, T. P., & Isometsä, E. T. (2002). Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. *The Journal of Clinical Psychiatry, 63*(2), 126–134.
- Moffitt, T. E., Caspi, A., Taylor, A., Kokaua, J., Milne, B. J., Polanczyk, G., & Poulton, R. (2010). How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. *Psychological Medicine, 40*(06), 899–909. <https://doi.org/10.1017/S0033291709991036>
- Moffitt, T. E., & the E-Risk Study Team. (2002). Teen-aged mothers in contemporary Britain. *Journal of Child Psychology and Psychiatry, 43*(6), 727–742.
<https://doi.org/10.1111/1469-7610.00082>

- Moffitt, T. E., Harrington, H., Caspi, A., Kim-Cohen, J., Goldberg, D., Gregory, A. M., & Poulton, R. (2007). Depression and generalized anxiety disorder: Cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of General Psychiatry*, 64(6), 651–660. <https://doi.org/10.1001/archpsyc.64.6.651>
- Mullard, A. (2016). FDA rejects first cognitive claim for antidepressant. *Nature Reviews Drug Discovery*, 15(5), 299–299. <https://doi.org/10.1038/nrd.2016.92>
- Muller, J., & Roberts, J. E. (2005). Memory and attention in obsessive-compulsive disorder: A review. *Journal of Anxiety Disorders*, 19(1), 1–28. <https://doi.org/10.1016/j.janxdis.2003.12.001>
- National Academies of Sciences, Engineering, and Medicine. (2015). *Enabling Discovery, Development, and Translation of Treatments for Cognitive Dysfunction in Depression: Workshop Summary*. Washington (DC): National Academies Press (US). Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK305332/>
- Newman, D. L., Moffitt, T. E., Caspi, A., Magdol, L., Silva, P. A., & Stanton, W. R. (1996). Psychiatric disorder in a birth cohort of young adults: Prevalence, comorbidity, clinical significance, and new case incidence from ages 11 to 21. *Journal of Consulting and Clinical Psychology*, 64(3), 552–562. <https://doi.org/10.1037/0022-006X.64.3.552>
- Odgers, C. L., Caspi, A., Bates, C. J., Sampson, R. J., & Moffitt, T. E. (2012). Systematic social observation of children’s neighborhoods using Google Street View: a reliable and cost-effective method. *Journal of Child Psychology and Psychiatry*, 53(10), 1009–1017. <https://doi.org/10.1111/j.1469-7610.2012.02565.x>

- Philipp, M., Maier, W., & Delmo, C. D. (1991). The concept of major depression. *European Archives of Psychiatry and Clinical Neuroscience*, 240(4–5), 258–265.
<https://doi.org/10.1007/BF02189537>
- Poulton, R., Moffitt, T. E., & Silva, P. A. (2015). The Dunedin Multidisciplinary Health and Development Study: overview of the first 40 years, with an eye to the future. *Social Psychiatry and Psychiatric Epidemiology*, 50(5), 679–693.
<https://doi.org/10.1007/s00127-015-1048-8>
- Rajput, S., Hassiotis, A., Richards, M., Hatch, S. L., & Stewart, R. (2011). Associations between IQ and common mental disorders: The 2000 British National Survey of Psychiatric Morbidity. *European Psychiatry*, 26(6), 390–395.
<https://doi.org/10.1016/j.eurpsy.2010.07.002>
- Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S. E., Murray, R. M., ... Moffitt, T. E. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. *The American Journal of Psychiatry*, 167(2), 160–9.
- Robins, L., Cottler, L., Bucholz, K., & Compton, W. (1995). *Diagnostic Interview Schedule for DSM-IV*. St. Louis: Washington University School of Medicine.
- Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine*, 44(10), 2029–2040. <https://doi.org/10.1017/S0033291713002535>
- Rogers, M. A., Kasai, K., Koji, M., Fukuda, R., Iwanami, A., Nakagome, K., ... Kato, N. (2004). Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neuroscience Research*, 50(1), 1–11.
<https://doi.org/10.1016/j.neures.2004.05.003>

Salmond, C. H., Menon, D. K., Chatfield, D. A., Pickard, J. D., & Sahakian, B. J. (2006).

Cognitive reserve as a resilience factor against depression after moderate/severe head injury. *Journal of Neurotrauma*, 23(7), 1049–58.

<https://doi.org/http://dx.doi.org/10.1089/neu.2006.23.1049>

Sattler, J. M. (2008). *Assessment of Children: Cognitive Foundations (5th edition)*. San Diego: Jerome M. Sattler, Publisher.

Schaefer, J. D., Caspi, A., Belsky, D. W., Harrington, H., Houts, R., Horwood, L. J., ... Moffitt, T. E. (2017). Enduring mental health: Prevalence and prediction. *Journal of Abnormal Psychology*. <https://doi.org/10.1037/abn0000232>

Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: Consistent over decades and around the world.

Schizophrenia Research, 150(1), 42–50. <https://doi.org/10.1016/j.schres.2013.07.009>

Scult, M. A., Knodt, A. R., Swartz, J. R., Brigidi, B. D., & Hariri, A. R. (2016). Thinking and feeling individual differences in habitual emotion regulation and stress-related mood are associated with prefrontal executive control. *Clinical Psychological Science*, 5(1), 150–157. <https://doi.org/10.1177/2167702616654688>

Scult, M. A., Paulli, A. R., Mazure, E. S., Moffitt, T. E., Hariri, A. R., & Strauman, T. J. (2017).

The association between cognitive function and subsequent depression: a systematic review and meta-analysis. *Psychological Medicine*, 47(1), 1–17.

<https://doi.org/10.1017/S0033291716002075>

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review.

Psychological Bulletin, 139(1), 81–132. <https://doi.org/10.1037/a0028727>

- Sørensen, H. J., Sæbye, D., Urfer-Parnas, A., Mortensen, E. L., & Parnas, J. (2012). Premorbid intelligence and educational level in bipolar and unipolar disorders: A Danish draft board study. *Journal of Affective Disorders, 136*(3), 1188–1191.
<https://doi.org/10.1016/j.jad.2011.12.007>
- Stavro, K., Pelletier, J., & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. *Addiction Biology, 18*(2), 203–213.
<https://doi.org/10.1111/j.1369-1600.2011.00418.x>
- Takayanagi, Y., Spira, A. P., Roth, K. B., Gallo, J. J., Eaton, W. W., & Mojtabai, R. (2014). Accuracy of reports of lifetime mental and physical disorders: Results from the Baltimore Epidemiological Catchment Area Study. *JAMA Psychiatry, 71*(3), 273–280.
<https://doi.org/10.1001/jamapsychiatry.2013.3579>
- Trouton, A., Spinath, F. M., & Plomin, R. (2002). Twins Early Development Study (TEDS): A multivariate, longitudinal genetic investigation of language, cognition and behavior problems in childhood. *Twin Research, 5*(5), 444–448.
<https://doi.org/10.1375/136905202320906255>
- Wechsler, D. (1974). *Manual for the Wechsler Intelligence Scale for Children, Revised*. New York, NY: Psychological Corp.
- Wechsler, D. (2008). *Wechsler Adult Intelligence Scale (4th ed.)*. San Antonio, TX: Pearson Assessment.
- Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., ... Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *The Lancet, 382*(9904), 1575–1586. [https://doi.org/10.1016/S0140-6736\(13\)61611-6](https://doi.org/10.1016/S0140-6736(13)61611-6)

- Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data.
American Journal of Epidemiology, 159(7), 702–706. <https://doi.org/10.1093/aje/kwh090>

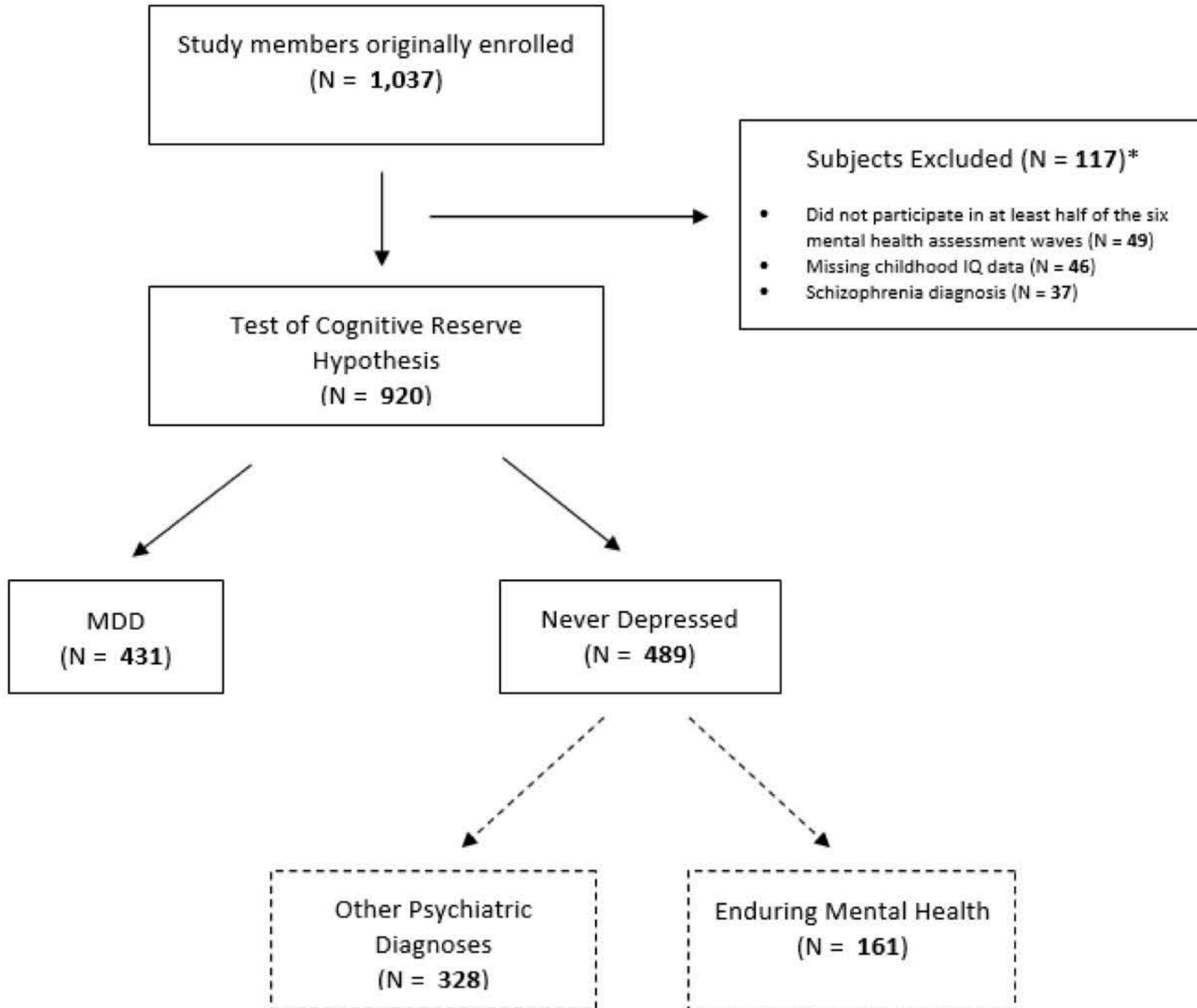
Table 1. Testing the “cognitive reserve” hypothesis: Between- and within-twin pair effects of childhood IQ on risk of depression at age 18 in the E-Risk Cohort

Effects	All Twins (<i>N</i> = 2,003)		MZ Twins (<i>N</i> = 1,124)	
	RR (95% CI)	p	RR (95% CI)	P
β_B	1.00 (0.99-1.00)	0.279	1.00 (0.99-1.01)	0.685
β_w	1.00 (0.99-1.01)	0.720	0.99 (0.97-1.01)	0.344

Notes. β_B represents the between-pair effects of mean childhood IQ (assessed at age 12) on risk of depression at age 18. β_w represents the effect of within-pair differences in childhood IQ, controlling for the effects of shared family environment and (in MZ twins) genetics. Sex was included in each model as a covariate.

Figure 1. Dunedin Study member flow diagrams for (A) our test of the cognitive reserve hypothesis and (B) our test of the cognitive scarring hypothesis.

A.



B.

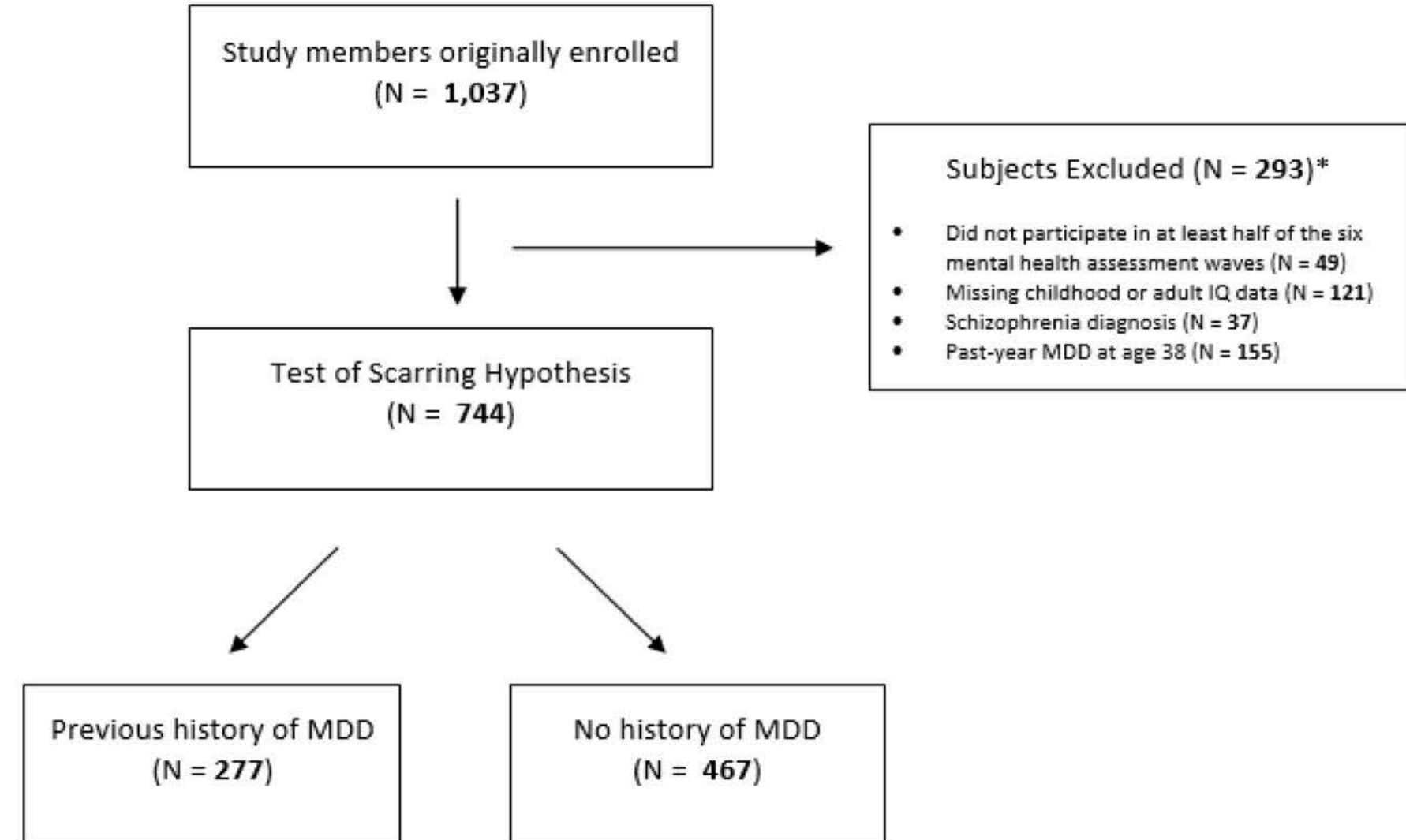


Figure 2. Mean (A) childhood IQ, (B) change in IQ from childhood to adulthood, and (C) subjective adult cognitive functioning by lifetime psychiatric comorbidity in the Dunedin Cohort.

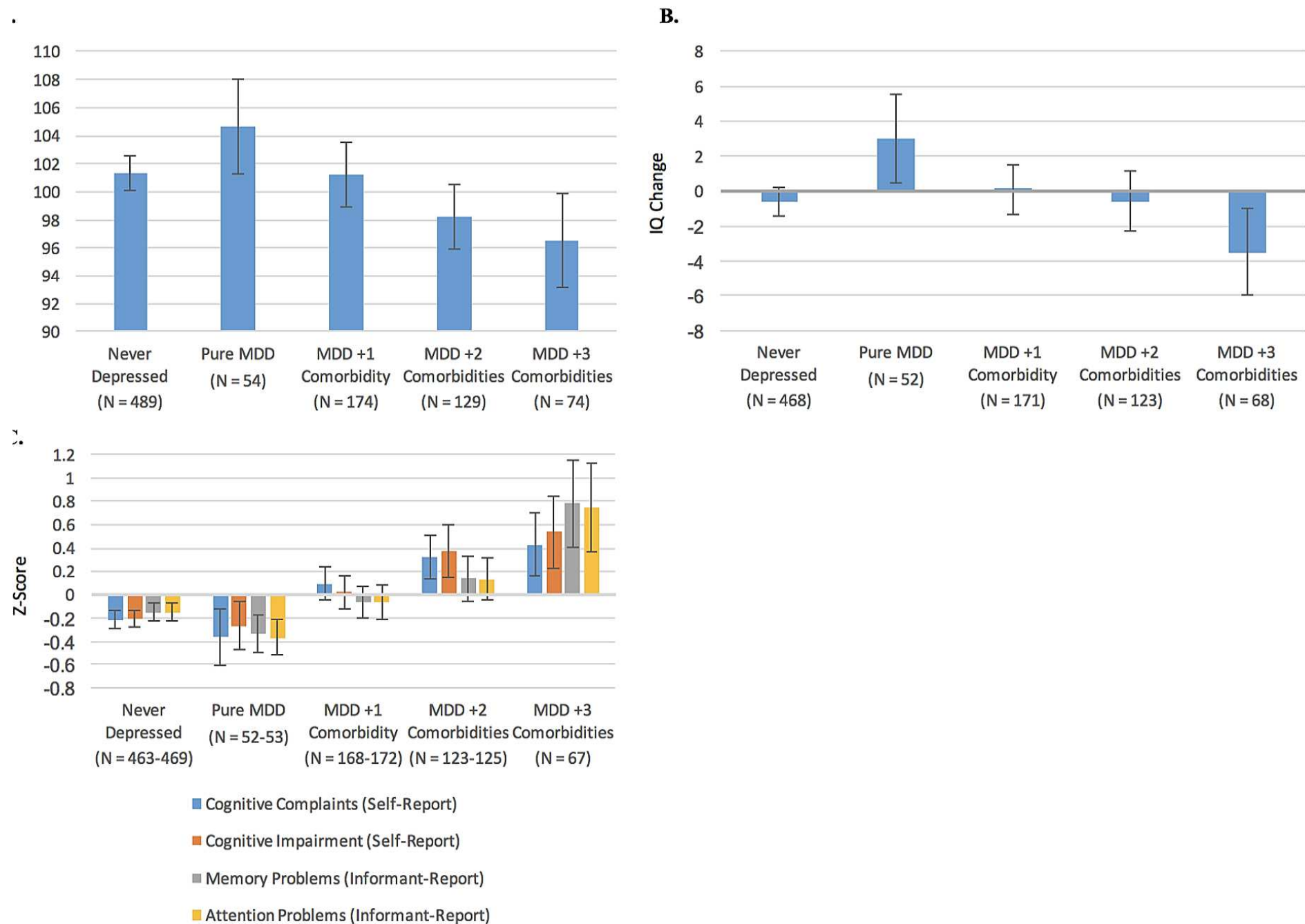


Table 2. Testing the “scarring hypothesis”: Cognitive functioning in Study members who were not diagnosed with past-year MDD at age 38, by lifetime diagnostic history.

Measure (Age at Assessment)	No History of MDD		Past History of MDD		<i>F</i>	p
	<i>N</i>	Mean (95% CI)	<i>N</i>	Mean (95% CI)		
Objective Measures						
WISC IQ (Age 7-11)	277	101.3 (99.8, 102.9)	467	101.6 (100.4, 102.8)	0.02	0.897
WAIS IQ (Age 38)	277	101.2 (99.5, 102.9)	467	101.0 (99.7, 102.3)	0.23	0.631
IQ Change	277	-0.14 (-1.27, 0.99)	467	-0.62 (-1.44, 0.20)	0.31	0.577
Subjective Measures						
<i>Self-Reported</i>						
Cognitive Complaints (Age 38)	277	0.11 (-0.01, 0.22)	467	-0.21 (-0.29, -0.13)	13.99	<0.001
Impairment (Age 38)	277	0.04 (-0.07, 0.16)	467	-0.20 (-0.27, -0.13)	13.33	<0.001
<i>Informant-Reported</i>						
Memory Problems (Age 38)	275	-0.02 (-0.13, 0.10)	460	-0.15 (-0.22, -0.07)	7.08	0.008
Attention Problems (Age 38)	275	-0.04 (-0.15, 0.07)	460	-0.15 (-0.23, -0.07)	6.04	0.014

Notes. This table includes only those Study members who (a) were not diagnosed with past-year MDD at age 38 and (b) had present data for adult IQ. The “no history of MDD” group represents Study members who had never met criteria for MDD. The “past history of MDD” group represents Study members who had met diagnostic criteria for MDD during a previous wave but no longer met criteria at age 38. Scores on objective measures are reported as IQ points (mean = 100, SD = 15). Scores on subjective measures were standardized in the full cohort to a mean of 0 and a standard deviation of 1. Means were compared across diagnostic groups through a series of one-way ANOVAs, controlling for sex.

Tables 3. Testing the “scarring hypothesis”: Change in IQ points from childhood to adulthood per standard deviation increase in each clinical indicator among Study members diagnosed with MDD.

Clinical Indicators	Change in IQ					
	b (SE)	b (SE)	b (SE)	b (SE)	b (SE)	b (SE)
Age of onset	-0.06 (-1.01, 0.88)					
Persistence/Recurrence		0.11 (-1.02, 1.24)				
Self-rated impairment			-0.33 (-1.29, 0.63)			
# of Symptom Criteria				-0.29 (-1.40, 0.82)		
Clinical Attention					0.26 (-0.89, 1.41)	
Psychiatric Comorbidity						-2.41*** (-3.68, -1.15)

Notes. This table displays coefficients and 95% confidence intervals from a series of separate regression equations predicting change in IQ from childhood (assessed at ages 7-11) to adulthood (age 38) as a function of each clinical indicator, controlling for sex. Ns for each regression ranged from 347 to 414. Clinical indicators were standardized to a mean of 0 and a standard deviation of 1 in the full cohort to facilitate comparison across indicators.

*** = $p < 0.001$

SUPPLEMENTARY MATERIALS TO SCHAEFER ET AL.,
IS LOW COGNITIVE FUNCTIONING A PREDICTOR OR CONSEQUENCE OF MAJOR
DEPRESSIVE DISORDER? A TEST IN TWO LONGITUDINAL BIRTH COHORTS

These Supplementary Materials contain additional details about the neuropsychological tests administered at ages 13 and 38 in the Dunedin Study. In addition, they contain supplemental tables to accompany the results of statistical analyses reported in the main article.

Measures of neuropsychological functioning

All testing occurred in the morning in two 50-min counterbalanced sessions. Dunedin Study members completed a small number of neuropsychological measures at age 13, and then a larger battery at age 38.

Neuropsychological functioning at age 13 years.

We assessed *executive functioning* with the following test:

Trails-B is a test of scanning and tracking, divided attention, and mental flexibility, which involves drawing lines to connect consecutively numbered and lettered circles, alternating between numbers and letters. Scores represent the time, in seconds, to complete the test. Lower scores are better (Army Individual Test Battery, 1944). Test-retest reliability=0.73-0.89.

We assessed *memory* with the following tests:

Rey Auditory Verbal Learning Test: Total Recall is a test of verbal learning and memory that involves a five-trial presentation of a 15-word list and a one- time presentation of an interference list. Four trials of the 15-word list were administered due to time constraints. The Total Recall indexes the total number of words (0–60) recalled over four trials (the sum of words recalled across trials 1–4). Higher scores are better (Lezak, 2004); Test-retest reliability=0.86.

Rey Auditory Verbal Learning Test: Delayed Recall indexes the total number of words from the original list (0–15) recalled after a 25–30 minute delay. Higher scores are better (Lezak, 2004). Test-retest reliability=0.80.

Neuropsychological functioning at age 38 years.

We assessed *executive functioning* with the following tests:

CANTAB Rapid Visual Information Processing: A' (A-prime), is a signal-detection measure that taps sustained attention, often called attentional vigilance. The participant scans for a 3-digit target sequence in a digit stream that is ongoing for 7 minutes, and responds whenever a target sequence is spotted. At the most difficult level, the participant scans simultaneously for two target sequences. Higher scores are better (Sahakian & Owen, 1992); Test-retest reliability=0.76.

CANTAB Rapid Visual Information Processing: Total False Alarms records impulsive jumping to respond too soon before the correct target digit sequence is complete. Because relatively few participants made numerous false alarms, this measure is categorical, coded 0=none, 1=1 false alarm, 2=2 or more false alarms. Lower scores are better (Sahakian & Owen, 1992); Test-retest reliability not available.

WAIS Working Memory Index was derived from the Arithmetic and Digit-span subtests. The Arithmetic subtest of WAIS requires working memory processes to be applied to orally presented verbal information. It involves numerical knowledge, short-term memory, attention, and concentration. Arithmetic problems are presented in story format. Performance requires holding information in short-term memory, accessing long-term memory to retrieve numerical rules of mathematical operation, and using the rules to manipulate the stored data. Items are arranged according to the level of difficulty and have time limits. The Digit-span subtest of WAIS is a test of memory span, attention/concentration, and ability to mentally manipulate information. The test requires listening to a sequence of digits read aloud and repeating them in forward, backward, and ascending order. Digit sequences range in length from 2 to 9 digits and

are presented in order of difficulty. Higher scores on the WAIS Working Memory Index are better (Wechsler, 2008); Test-retest Reliability=0.90

Wechsler Memory Scale-III: Months of the Year Backwards Test is a test of attention and tracking. It requires reciting the months of the year in backwards order, starting with December. Responses were scored according to the instructions in the WMS-III manual. Scores ranged from 1 (poor performance) to 5 (good performance) and reflect both accuracy and speed. Higher scores are better (Wechsler, 1997); Test-retest Reliability=0.80

Trails-B is a test of scanning and tracking, divided attention, and mental flexibility, which involves drawing lines to connect consecutively numbered and lettered circles, alternating between numbers and letters. Scores represent the time, in seconds, to complete the test. Lower scores are better (Army Individual Test Battery, 1944). Test-retest reliability=0.73-0.89.

We assessed *memory* with the following tests:

CANTAB Paired Associates Learning: First Trial Memory Score is a test of visual memory and new learning. Boxes are displayed on the screen and are opened in a random order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time, and the subject must touch the box where the pattern was originally located. If the subject makes an error, the patterns are re-presented to remind the subject of their locations. The difficulty level increases through the test. The number of patterns increases across eight stages (i.e., two 1-pattern stages, two 2-pattern stages, two 3-pattern stages, one 6-pattern stage, one 8-pattern stage), which challenges even very able subjects. For each stage, up to 10 trials are presented until all the patterns are located correctly. For the First Trial Memory Score, the number of patterns correctly located after the first trial of each stage is summed across the

stages completed (range 0–26, with 26 meaning that all the patterns were correctly located for all stages the first time). Higher scores are better (Sahakian & Owen, 1992); Test-retest reliability=0.87.

CANTAB Paired Associates Learning: Total Errors is based on the same protocol as above but considers the total number of errors (with an adjustment for each stage not attempted due to previous failure). Lower scores are better (Sahakian & Owen, 1992); Test-retest reliability=0.64.

Wechsler Memory Scale-III: Verbal Paired Associates Total Recall is a test of verbal learning and memory. Eight pairs of unrelated words (e.g., hat-sofa) are read aloud and followed by a recall task (one of the words from each word pair is given, and the associated word must be recalled). Four trials of the eight word-pairs are presented. Presentation of the word-pairs is randomized across trials. The total recall score represents the total number of words (0–32) recalled across four trials. Higher scores are better (Wechsler, 1997); Test-retest reliability=0.75.

Wechsler Memory Scale-III: Verbal Paired Associates Delayed Recall is based on the same protocol as above but represents the total number of words (0–8) recalled after a 25–35 minute delay. Higher scores are better (Wechsler, 1997); Test-retest reliability=0.73.

Rey Auditory Verbal Learning Test: Total Recall is a test of verbal learning and memory that involves a five-trial presentation of a 15-word list and a one- time presentation of an interference list. Four trials of the 15-word list were administered due to time constraints. The Total Recall indexes the total number of words (0–60) recalled over four trials (the sum of words recalled across trials 1–4). Higher scores are better (Lezak, 2004); Test-retest reliability=0.86.

Rey Auditory Verbal Learning Test: Delayed Recall indexes the total number of words from the original list (0–15) recalled after a 25–30 minute delay. Higher scores are better (Lezak, 2004). Test-retest reliability=0.80.

Table S1. Testing the “cognitive reserve hypothesis”: Neuropsychological test performance of Study members who did and did not receive a diagnosis of MDD by age 38.

Measures (All Administered at Age 13)	Never Depressed		Ever Depressed		Poisson Regression Results	
	<i>N</i>	Mean (95% CI)	<i>N</i>	Mean (95% CI)	IRR (95% CI)	<i>p</i>
<i>Executive Functioning</i>						
Trails B (time in seconds)	368	35.5 (33.6, 37.3)	286	37.5 (35.5, 39.4)	1.00 (1.00, 1.01)	0.053
<i>Memory</i>						
Rey Auditory Verbal Learning Test -- Total words recalled	375	40.6 (39.9, 41.3)	290	41.3 (40.5, 42.1)	0.99 (0.96, 1.02)	0.551
Rey Auditory Verbal Learning Test -- Delayed recall	374	9.9 (9.7, 10.2)	289	10.0 (9.7, 10.4)	1.00 (0.99, 1.01)	0.733

Notes. This table includes Study members from the full analytic sample (see **Figure 1A**) who completed neuropsychological testing at age 13. To ensure that cognitive functioning at age 13 was being used to predict *future* MDD, Study members who received a diagnosis of MDD prior to age 18 were excluded from this analysis. The “Never Depressed” group represents Study members who did not ever meet criteria for MDD between the ages of 18 and 38. The “Ever Depressed” group represents Study members who did meet diagnostic criteria for MDD during this same period. Relative risk (IRR) of MDD was calculated using a modified Poisson regression model with robust standard errors (Zou, 2004). Significant group differences ($p < 0.05$) are shown in **bold**.

Table S2: Testing the “scarring hypothesis”: Neuropsychological test performance of Study members who were not diagnosed with past-year MDD at age 38, by lifetime diagnostic history.

Measures (All Administered at Age 38)	Never Depressed		Ever Depressed		<i>F</i>	p
	<i>N</i>	Mean (95% CI)	<i>N</i>	Mean (95% CI)		
<i>Executive Functioning</i>						
Rapid Visual Processing -- A prime	271	0.91 (0.91, 0.92)	458	0.91 (0.91, 0.92)	0.01	0.916
Rapid Visual Processing -- False alarms	271	0.23 (0.18, 0.30)	460	0.25 (0.20, 0.30)	0.11	0.743
WAIS-IV Working Memory Index	277	103.5 (101.6, 105.4)	467	104.4 (103.0, 105.7)	0.03	0.867
WMS-III Months of the Year Backwards	276	3.12 (2.96, 3.28)	467	3.12 (3.00, 3.25)	1.93	0.165
Trails B (time in seconds)	277	63.9 (61.5, 66.3)	466	63.4 (61.6, 65.2)	0.81	0.367
<i>Memory</i>						
CANTAB Paired Associates -- First Trial	273	20.2 (19.8, 20.7)	460	20.3 (20.0, 20.6)	0.21	0.649
CANTAB Paired Associates -- Total Errors	273	12.3 (9.8, 14.8)	461	11.0 (9.8, 12.1)	1.83	0.176
Verbal Paired Associates -- Total N correct	276	17.1 (16.1, 18.1)	467	15.6 (14.9, 16.4)	3.07	0.080
Verbal Paired Associates -- Delayed recall total	276	5.6 (5.3, 5.9)	465	5.1 (4.8, 5.3)	4.40	0.036
Rey Auditory Verbal Learning Test -- Total words recalled	275	38.7 (37.8, 39.6)	467	37.1 (36.4, 37.8)	1.32	0.252
Rey Auditory Verbal Learning Test -- Delayed recall	276	9.4 (9.1, 9.8)	467	9.0 (8.7, 9.3)	0.11	0.745

Notes. This table includes only those Study members who (a) completed neuropsychological testing at age 38, (b) were not diagnosed with past-year MDD at age 38 and (b) had present data for adult IQ. The “no history of MDD” group represents Study members who had never met criteria for MDD. The “past history of MDD” group represents Study members who had met diagnostic criteria for MDD during a previous wave but no longer met criteria at age 38. Means were compared across diagnostic groups through a series of one-way ANOVAs, controlling for sex. Significant group differences ($p < 0.05$) are shown in **bold**.

References

- Army Individual Test Battery. (1944). *Manual and directions for scoring*. Washington, DC: War Department.
- Lezak, M. D. (2004). *Neuropsychological Assessment* (4th ed.). New York, NY: Oxford University Press.
- Sahakian, B. J., & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *Journal of the Royal Society of Medicine*, 85, 399–402.
- Wechsler, D. (1997). *Wechsler memory scale* (3rd ed.). San Antonio, TX: Psychological Corporation.
- Wechsler, D. (2008). *Wechsler Adult Intelligence Scale (4th ed.)*. San Antonio, TX: Pearson Assessment.
- Zou, G. (2004). A modified Poisson regression approach to prospective studies with binary data. *American Journal of Epidemiology*, 159(7), 702–706. <https://doi.org/10.1093/aje/kwh090>